Lysophosphatidic Acid Mediates Myeloid Differentiation within the Human Bone Marrow Microenvironment.

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Public Summary:
Hematopoietic stem and progenitor cells (HSPC) in the bone marrow can differentiate into multiple lineages of mature blood cells including such highly specialized cells as red blood cells, macrophages and lymphocytes. To a large extent “fate” or “what to be” decisions of HSPC are controlled by unique signals within the bone marrow microenvironment. Signals required for the generation of a red blood cell are different to those needed for the generation of lymphocyte; therefore spatial separation of different hematopoietic lineages in the bone marrow must be required. Mechanisms controlling spatial and functional compartmentalization within hematopoietic organs are poorly understood. Understanding how these molecular signals function in normal and disease conditions could provide us with the capacity to better control and direct HSPC differentiation, thereby improving the accessibility of transplantation to many patients. We have discovered that lysophosphatidic acid (LPA), a lipid molecule that stimulates cell growth and migration, induces differentiation of HSPCs down the myeloid lineage, into cell types including monocytes, granulocytes, and megakaryocytes/platelets, but has little or no effect on differentiation of HSPC towards lymphocytes. LPA exerts its effects on myeloid cell development by directly stimulating an early common myeloid progenitor - an intermediate cell made during myeloid differentiation of HSPC. LPA also plays a protective role inhibiting myeloid progenitor cell death. When looking at tissue sections of the bone marrow, we found that PPAP2A, an enzyme that is responsible for the break down of LPA is expressed at high levels near the osteoblasts lining the bone and lower levels towards the blood vessels infiltrating the bone marrow. In contrast the enzyme autotaxin, which is involved in the synthesis of LPA, is expressed at high levels near the blood vessels and low levels near the bone. The presence of these two enzymes creates compartments within the bone marrow that are either more or less permissive for myeloid differentiation of HSPC. Our functional studies may explain previously made observations indicating that proliferating myeloid colonies are often located near small blood vessels in the bone marrow while lymphocytes are often produced close to the osteoblastic layer. It is plausible that isolation of primary cells with different LPA-producing and -inactivating potential from bone marrow samples or generating these populations from human embryonic stem cells will significantly improve or current protocols for HSPC culture in vitro. A number of pharmacological compounds that can directly target those enzymes and or/ LPA receptors are currently being developed by pharmaceutical industry and therefore may soon become clinically available. These findings describe a novel regulator of HSCP differentiation and therefore offer a tool for manipulating the human blood forming program both in the dish and in patients.

Scientific Abstract:
Lysophosphatidic acid (LPA) is a pleiotropic phospholipid present in the blood and certain tissues at high concentrations; its diverse effects are mediated through differential, tissue specific expression of LPA receptors. Our goal was to determine if LPA exerts lineage-specific effects during normal human hematopoiesis. In vitro stimulation of CD34+ human hematopoietic progenitors by LPA induced myeloid differentiation but had no effect on lymphoid differentiation. LPA receptors were expressed at significantly higher levels on Common Myeloid Progenitors (CMP) than either multipotent Hematopoietic Stem/Progenitor Cells (HSPC) or Common Lymphoid Progenitors (CLP) suggesting that LPA acts on committed myeloid progenitors. Functional studies demonstrated that LPA enhanced migration, induced cell proliferation and reduced apoptosis of isolated CMP, but had no effect on either HSPC or CLP. Analysis of adult and fetal human bone marrow sections showed that PPAP2A, (the enzyme which degrades LPA) was highly expressed in the osteoblastic niche but not in the perivascular regions, whereas Autotaxin (the enzyme that synthesizes LPA) was expressed in perivascular regions of the marrow. We propose that a gradient of LPA with the highest levels in peri-sinusoidal regions and lowest near the endosteal zone, regulates the localization, proliferation and differentiation of myeloid progenitors within the bone marrow marrow.

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